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202 • 408 • 4000
FACSIMILE 202 • 408 • 4400

WRITER'S DIRECT DIAL NUMBER:

(202) 408-4090

February 2, 2000

ATTORNEY DOCKET NO. 7414.0018

Box PATENT APPLICATION
Assistant Commissioner for Patents
Washington, D.C. 20231

Re: New Non-Provisional U.S. Patent Application
Title: APPARATUS AND METHOD FOR EJECTING
SAMPLE WELL TRAYS
Inventors: Hon S. SHIN, Jew W. NGUI, Adrian FAWCETT
Kenneth P. CHAO, Gary L. BORDENKIRCHER,
Jessica BARZILAI and Donald R. SANDELL

Sir:

We enclose the following papers for filing in the United States Patent and Trademark Office in connection with the above patent application.

1. Application - 44 pages (including a cover page), including five (5) independent claims and thirty-nine (39) claims total.
2. Drawings - twelve (12) sheets of informal drawings (Figures 1-13C).
3. The Commissioner is hereby authorized to charge the \$1,188.00 filing fee or any additional filing fees due and any other fees due under 37 C.F.R. § 1.16 or § 1.17 during the pendency of this application to our Deposit Account No. 06-0916.

This application is being filed under the provisions of 37 C.F.R. § 1.53(f). Applicants await notification from the Patent and Trademark Office of the time set for filing the Declaration.



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Enclosures

UNITED STATES PATENT APPLICATION
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FOR

APPARATUS AND METHOD FOR EJECTING SAMPLE WELL TRAYS

BACKGROUND OF THE INVENTION

Field of the Invention

5 The present invention relates to an apparatus and method for ejecting sample well trays from a heating apparatus for biological samples. The apparatus improves the process of removing a sample well tray from a sample block after the cover of the heating apparatus is opened.

Description of the Related Art

10 Biological testing has become an important tool in detecting and monitoring diseases. In the biological field, thermal cycling is utilized in order to perform polymerase chain reactions (PCR) and other reactions. To amplify DNA (Deoxyribose Nucleic Acid) using the PCR process, a specifically constituted liquid reaction mixture is cycled through a PCR protocol including several different temperature incubation periods. An aspect of the PCR process is the concept of thermal cycling: alternating steps of melting DNA, annealing short primers to the resulting single strands, and extending those primers to make new copies of double-stranded DNA. During thermal cycling, it is desirable that the temperature of each of a plurality of sample wells are substantially identical. In addition, it is important that condensation is avoided on the caps or other covering for the sample wells.

15 20 A common method of inhibiting condensation on the top of the sample wells is to provide a heated platen for pressing down on the tops or caps of the sample well trays. The platen is typically included as part of a cover and is typically metal. The platen

transfers heat to the caps of the sample wells, thereby inhibiting condensation. In addition, the platen presses down on the sample wells so that the sample well outer conical surfaces are pressed firmly against the mating surfaces on the sample block. This increases heat transfer to the sample wells, and assists in providing a more uniform distribution of sample well temperatures. The platen also prevents thermal leakage from the interior of the device. Examples of a system with a platen and heated cover are described in U.S. Patent Numbers 5,475,610, 5,602,756, and 5,710,381, all of which are assigned to the assignee of the present invention, and the contents of which are all hereby incorporated by reference herein.

The sample well trays can stick inside of the sample block due to expansion of the sample well trays and due to the force imparted on the trays by the thermal cycler cover. A considerable force may be required to unstick the sample wells and tray from the sample block and remove the tray. Unfortunately, laboratory robotic systems for removing sample well trays can sometimes have difficulty generating sufficient force to remove the sample well trays from the sample block. With the increase in the popularity of laboratory automation, it is particularly desirable to make the thermal cyclers more compatible to robotic removal of the sample well trays from the sample block. It is also desirable to increase the throughput of these devices.

SUMMARY OF THE INVENTION

The advantages and purposes of the invention will be set forth in part in the description which follows, and in part will be apparent from the description, or may be

appreciated by practice of the invention. The advantages and purposes of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

In one aspect, the invention includes a heating apparatus for biological samples. The heating apparatus of the present invention includes a cover, a sample block having a plurality of openings in a top portion thereof for receiving a sample well tray having a plurality of sample wells, and an urging mechanism. The urging mechanism is positionable between the sample block and the sample well tray to urge the sample well tray away from the sample block when the cover is moved from a closed position toward an open position. The cover imparts a downward force on the top of the sample well tray to press the sample wells into the openings of the sample block when the heated cover is moved toward a closed position. The urging mechanism imparts an upward force on the sample well tray. The downward force imparted by the heated cover is sufficient to retain the sample well tray against the sample block when the cover is in the closed position. In one embodiment, the urging mechanism is attached to the sample block. In an alternate embodiment, the urging mechanism is attached to a sample well tray holder.

In another aspect, the invention includes a system for urging a sample well tray away from a sample block. The system includes a sample block having a plurality of openings for receiving sample wells of a sample well tray therein, and at least one

urging mechanism interposed between the sample block and sample well tray to urge the sample wells away from the openings in the sample block.

5 In a further aspect of the invention, the invention includes a method of manipulating a sample well tray with respect to a sample block. The method includes the step of providing an initial downward force on a sample well tray, the initial downward force pressing sample wells of the sample well tray into openings on a top surface of a sample block; and the step of providing an upward force on the sample well tray. The method may further include the steps of reducing the initial downward force on the sample well tray, and urging the sample well tray from the sample block by an upward force between the sample well tray and the sample block.

10 In a further aspect of the invention, the invention includes a mechanism for urging a sample tray away from a sample block in a biological sample heating device. The mechanism includes a spring positioned between the sample block and sample tray. The spring has a sufficient force in a compressed state to move the sample tray in a direction substantially away from the sample block in response to opening a cover away from the sample tray.

15 It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention. In the drawings,

Fig. 1 shows a perspective view of a thermal cycler system according to the invention, with a cover in an open position;

Fig. 2 shows a close-up perspective view of a sample block and sample well tray of the system of Fig. 1;

Fig. 3 shows a partial top view of the sample block of Fig. 2 with the sample well tray removed;

Fig. 4 shows a sectional view of the sample block along line IV-IV of Fig. 3;

Fig. 5 shows a sectional view of the sample block along line V-V of Fig. 3;

Fig. 6 shows a perspective view of the sample block of Fig. 3;

Fig. 7 shows a sectional view of the sample well tray and sample block along line VII-VII of Fig. 2;

Fig. 8 shows a sectional view of the sample well tray and sample block along line VIII-VIII of Fig. 2;

Figs. 9A, 9B, and 9C show a side view, a top view, and a perspective view, respectively, of an ejection spring for the thermal cycler of Fig. 1;

Figs. 10A, 10B, and 10C show a side view, a top view, and a perspective view, respectively, of a second ejection spring for the thermal cycler of Fig. 1;

Fig. 11 shows a perspective view of a sample well tray, sample well tray holder, and sample block according to a second embodiment of the present invention;

Fig. 12 shows a perspective view of the apparatus of Fig. 11 including a cover and a base; and

Fig. 13 shows a schematic illustrating the operation of the apparatus of Figs. 11-12.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Reference will now be made in detail to the present preferred embodiments of the invention, examples of which are illustrated in the accompanying drawings.

Wherever possible, the same reference numbers will be used throughout the drawings to refer to the same or like parts.

In accordance with the present invention, a heating apparatus for biological samples is provided. In one embodiment of the present invention, the apparatus includes a heated cover, a sample block having a plurality of openings, a sample well tray or plate having a plurality of sample wells, and an urging mechanism positioned between the sample block and the sample well tray to urge the sample well tray away from the sample block when the heated cover is moved from a closed position to an open position. As embodied herein and shown in Figs. 1-10, the heating apparatus 10 for biological samples includes a heated cover 12, a sample block 14, a sample well tray 16, and an urging mechanism 18.

5 The heating apparatus 10 may be any type of conventional heating device for thermally heating biological samples. In the embodiment shown in Figs. 1-10, the heating apparatus is a thermal cycler, specifically, a dual 384-well PE Biosystem 9700 thermal cycler system sold by PE Biosystems. The thermal cycler 10 shown in the first embodiment uses two 384-well sample well trays 16, however, the present invention is suitable with any of the other common configurations, such as a single 384-well configuration, a dual 96-well configuration, a single 96-well configuration, or a 60-well configuration. The present invention is also suitable with other configurations with any number of sample wells ranging from one sample well to several thousand sample wells. The specific type of heating apparatus is not a part of the instant invention, and is shown for purposes of illustration only. The present invention is suitable for any type of heating apparatus in which sample wells are pressed into a sample block by a cover. The present invention is especially suitable for use in a heating apparatus with a heated cover.

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15 Although the description and Figures discuss trays with sample wells, the present invention is suitable for use with sample trays that do not include wells. These trays may have a flat surface on which a sample of biological material is placed. The flat surface on which the sample is placed may be similar to a microscope slide for a sample. In this type of sample tray, a liquid may be dropped onto the tray at a plurality of positions, and then a film or cover positioned on the top surface of the tray over the samples. Alternately, a sample tray may include a porous material such a frit on the top surface, instead of sample wells, for holding samples of biological material. Therefore,

although the description refers to sample well trays throughout, it should be understood that the present invention is also suitable for sample trays that do not have sample wells.

5 In accordance with the present invention, the heating apparatus includes a heated cover. As embodied herein and shown in Figs. 1-10, the heated cover 12 is located above the sample block 14 and sample well tray 16. The heated cover is operable between an open position, as shown in Fig. 1, and a closed position where the heated cover is placed over the sample block and sample well tray. The heated cover is maintained in an open position during insertion of the sample well tray into the sample block, and is then closed during operation of the heating apparatus, i.e., thermal cycling. In the open position, the heated cover does not engage the top of the sample well tray 16. In a closed position, the heated cover 12 presses down on the top portion of the sample well tray 16, thereby providing a downward force on the sample well tray.

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20 The top portion of each sample well of sample well tray 16 is typically defined by a cap, adhesive film, heat seal, or gap pad. In one embodiment of the present invention, a gap pad (not shown) is provided between a platen of the heated cover and the top surface of the sample well tray. The gap pad improves the distribution of the downward force on the top of the sample wells. In one embodiment, the gap pad is a MJ Research "Microseal P Type" silicon rubber plate. The gap pad will typically adhere to the platen. The gap pad may be used by itself, or in conjunction with an adhesive film or heat-sealed film. The type of cover for the sample well depends on the specific application and is not important for the purpose of the present invention. Alternately,

the gap pad may be used in conjunction with caps on the top portion of the sample wells. The caps may be connected in strips, or may be individually provided as separate, unconnected caps for each sample well. Alternately, caps may be used without the gap pad. Because all of these methods can be referred to as "capping" the sample wells, the remainder of the specification will refer to the structure immediately over the sample wells as a cap, regardless of whether it is a film, pad, or cap. The basic concepts of the invention are equally applicable on each of these arrangements.

The heated cover reduces heat transfer from the liquid sample by evaporation. The heated cover also reduces the likelihood of cross contamination by keeping the insides of the caps dry, thereby preventing aerosol formation when the wells are uncapped. The heated cover maintains the caps above the condensation temperature of the various components of the liquid sample to prevent condensation and volume loss of the liquid sample.

The heated cover may be of any of the conventional types known in the art. For example, in one preferred embodiment, the heated cover is physically actuated to and from a closed position by a motor. In another typical embodiment, the heated cover is slid into and out of a closed position by manual physical actuation. The heated cover typically includes at least one heated platen (not shown) for pressing against the top surface of the sample well trays. Details of the heated covers and platens are well known in the art, and are described for example in U.S. Patent Numbers 5,475,610, 5,602,756, and 5,710,381, all of which are assigned to the assignee of the present invention, and the contents of which are all hereby incorporated by reference herein.

While the present invention is described for use with a heated cover, the present invention also performs suitably with a cover which is not heated.

5 In accordance with the present invention, the heating apparatus includes at least one sample block and corresponding sample well tray. As embodied herein and shown in Figs. 1-10, in one embodiment, the sample block 14 includes a plurality of openings 20 in a top portion thereof for receiving sample wells of the sample well tray. In the embodiment shown, each of the sample block openings may have a conical shape which is sized to fit with a sample well of a sample well tray. The sample block openings may be other shapes such as cylindrical or hemispherical, depending on the shape of the mating sample wells. Sample blocks are well known in the art. Sample blocks may be a variety of materials, although metals such as aluminum or aluminum alloy are often preferred. The sample block is typically machined out of a solid block of material, however casting and other techniques are also well known. It is desirable that the sample block exhibits a substantially uniform temperature across the sample well openings 20, and that the openings maintain close tolerances with the sample wells that are inserted therein.

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20 The sample blocks shown in the embodiment of Figs. 1-10 have 384 openings arranged in a 16 x 24 array, however, any number of openings may be provided. Other common configurations include 96 and 60-well sample blocks, although the present invention is suitable for sample well trays having anywhere from one sample well to several thousand sample wells. Sample block openings 20 are positioned in a grid-like fashion on a top surface 22 of the sample block 14. The openings 20 are defined by a

5 conical side wall 24 and a bottom wall surface 26 as best shown in Figs. 5 and 7. The conical side wall 24 may slant at any appropriate angle known in the art. The size and shape of the openings shown in the drawings is by way of example only. Other designs having a different arrangement of sample wells are equally suitable with the present invention.

Sample block 14, as shown in Fig. 7, may include a bottom flange portion 28 for resting on the base 40 of the heating apparatus or any other alternate design. In one exemplary apparatus, a compression seal (not shown) may be provided between the flange portion 28 and base 40. The sample block of the present invention further includes the provision of portions engageable with an urging mechanism of the present invention. The engageable portions of the sample block will be described in greater detail later in the specification.

As embodied herein and shown in Figs. 1-10, in one embodiment, the sample well tray 16 includes a plurality of sample wells 42 in a top surface 44 thereof, as best shown in Fig. 7. Sample well trays suitable for the present invention are well known in the art, and are also referred to as sample well plates. The present invention is flexible so that virtually any type of sample well tray may be utilized. The sample wells 42 shown in the Figures are of a conventional conical design known in the art. The sample wells may be of a variety of other shapes such as cylindrical or hemispherical.

Each sample well 42 can hold a predefined volume of liquid sample. In one embodiment of the present invention, each sample well has a total volume of approximately 30 μ l and a working volume of approximately 20 μ l. In the example shown

in Figs. 1-10, the sample wells have a diameter of approximately 2.20mm and a depth of approximately 8.0mm. The volume and dimensions of the wells can be varied depending on the specific application, as well as depending upon the number of sample wells for the sample well tray. For example, a 384-well sample well tray will typically have a smaller sample well volume than a 96-well sample well tray. The sample well tray may be made out of any of the conventional materials such as polypropylene that are typically used in sample well trays that will undergo thermal cycling of biological samples. Although the Figures illustrate the sample wells being integrally formed as part of the sample well tray, the present invention is also suitable with a sample tray where the wells are individual tubes that may be individually detached from the tray. Alternately, the tubes may be connected together in sets of rows or columns.

The sample wells 42 are designed to closely mate with the conical side walls 24 of the sample block, particularly after the heated cover applies a downward force on the sample well tray. Fig. 7 shows the spacing between sample well tube walls 46 and the sample block side walls 24 in exaggerated form for illustration purposes only. Upon closing the cover so that the platen of the cover presses onto the caps on the top of the sample well tray, any gaps between the sample well walls 46 and the sample block side walls 24 should be greatly reduced or eliminated altogether. The close mating of the sample wells in the sample block openings 20 after closing the cover improves the heat transfer rate between the sample block 14 and the sample well tray 16. Because the sample well tray is typically made of a plastic material that is slightly deformable, the sample wells of the sample well tray will also slightly deform to match the shape of the

sample block openings 20. This ensures that the sample wells of the sample well tray will closely fit against the sample block to enhance the temperature uniformity of the sample wells of the sample well tray.

5 However, when the sample well tray 16 is urged downward by the heated cover 12, the sample well tube walls 46 impart a force on the inside surface of the sample block side walls 24. Even after the heated cover is opened so that the platen is no longer pressed against the sample well tray, the sample wells 42 of the sample well tray have a tendency to stick inside of the sample block openings 20. A significant force may be required to loosen the sample well tray 16 from the sample block 14.

10 In the typical prior art arrangement utilizing manual removal of the sample well tray from the sample block, an operator may need to use additional tools and significant effort to unstick the sample well tray from the sample block after the thermal cycling operation is completed. In order to loosen the sample well tray from the sample block, an operator typically grasps the sides of the sample well and imparts a rocking motion on the sample well tray while also pulling upward. The operation of manually loosening the sample wells from the sample well block openings may take up valuable time, thereby decreasing the throughput and effectiveness of the thermal cycling operation and increasing the amount of time for each sample. If the sample well trays are being robotically removed, instead of manually removed in a typical prior art arrangement, the consequences of the sticking between the sample well tray and the sample block may be even more dramatic. Robots used for sample well tray removal typically only generate very weak linear forces. Robots typically are unable to impart the rocking

motion which is helpful in removing the sample well trays from the sample block openings. Because the robots are typically limited to linear motions, instead of rotational motion, a much higher force is required in order to loosen the sample well tray from the sample block. The linear robot-generated forces are frequently inadequate to overcome the initial sticking force, therefore, the sample well tray may remain stuck in the sample block. Therefore, an operator may need to loosen the sample well tray from the sample block by manually prying the sample well tray from the sample block. Alternately, robots may be designed which are capable of imparting a rotational force on the sample well trays, however, these robots will typically be larger, slower, more complex, and more expensive than existing robots.

In order to overcome these drawbacks, the present invention includes an urging mechanism for urging the sample well tray away from the sample block. The urging mechanism tends to overcome the initial sticking force of the sample well tray in the sample block so that the sample well tray is loosened from the sample block without substantial manual or robotic assistance. The provision of the urging mechanism of the present invention reduces the need for an operator to help unstick the sample well tray from the sample block, saving time, and reducing costs. Additionally, the robots used for automated handling do not need to be made unnecessarily more powerful and bulky, thereby saving cost and space. The urging mechanism of the present invention may have a variety of designs, one of which is shown in the embodiment of Figs. 1-10.

In one embodiment shown in Figs. 1-10 of the present invention, the present invention includes urging mechanism 18 positioned between the sample block 14 and

the sample well tray 16 to urge the sample well tray away from the sample block when the heated cover is moved from the closed position to an open position. In the embodiment shown in Figs. 1-10, the urging mechanism comprises a plurality of first springs 50 and a plurality of second springs 60, as best shown in Fig. 2. The urging mechanism shown in Figs. 1-10 is by way of example only. The urging mechanism of the present invention is not limited to the example shown in the Figures.

As embodied herein and best shown in Fig. 7, the first springs 50 are positioned in a cylindrical spring opening 52 of the sample block in one embodiment of the present invention. The cylindrical opening 52 is defined by the side surfaces 54 and end surface 56 of the cylindrical opening, as best shown in Fig. 7. Alternately, the springs may be positioned on the top surface of the sample block without the provision of a cylindrical opening, depending on the amount of unsupported spring length.

Although the urging mechanism shown in Fig. 7 is a helical compression spring, a variety of other types of urging mechanisms may be utilized. For example, a variety of other types of springs such as leaf springs, conical helical springs, and other springs which will impart an axial force when compressed are suitable with the present invention. In addition, other spring-like devices suitable for use include, for example, elastomeric spring members, air cylinders, fluid cylinders, dampeners, belleville washers, and electrical solenoids. Any other suitable device that may be interposed in the system for imparting an upward force on the sample well tray may be used. The urging mechanism merely needs to be designed so that it creates sufficient force to overcome the sticking force between the sample well tray and the sample block upon

opening of the cover. The urging mechanism should loosen the sample well tray from the sample block so that the sample well tray can be easily removed either robotically or manually. If a spring is used, the size and spring constant of the spring must be selected so an adequate force is imparted by the spring on the sample well tray.

5 In the embodiment shown in Figs. 1-10, one end of first spring 50 abuts against the end surface 56 of cylindrical opening 52 in the sample block 14, as best shown in Fig. 7. The opposite end of spring 50 engages the lower surface 58 of the sample well tray 16. Although the Figures show the end surface 56 and lower surface 58 as being flat, other configurations may be used in order to more securely engage the spring. For example, the end surface 56 of the cylindrical opening or the lower surface 58 of the sample well tray may include grooves to closely fit the interior and/or exterior of the spring. When the spring 50 is compressed by the sample well tray, the spring 50 will impart an upward force on the sample well tray 16.

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20 In the embodiment shown in the Figures, a plurality of springs are provided. In Figs. 1-10, the urging mechanism 18 includes a plurality of first springs 50 and a plurality of second springs 60. The springs are positioned around an outer peripheral surface 62 of the sample block outside of the rectangular grid of sample block openings 20, as best shown in Fig. 2. In one embodiment, six first springs 50 are positioned on each longitudinal side (defined as the side with the greater number of sample well openings, for example, the side with twenty-four sample block openings in Fig. 2) of the outer peripheral top surface 62 of the sample well block.

5 A set of second springs 60 are positioned on each lateral side (defined as the side with the lesser number of sample well openings, for example, the side with sixteen sample block openings in Fig. 2) of the outer peripheral top surface 62 of the sample block outside of the grid of sample block openings. In the embodiment shown in Fig. 2, the second springs 60 are positioned on projections 70 that extend outward from the rectangular array of sample block openings on each lateral side of the top surface. In the Fig. 2 embodiment, two second springs 60 are located on each lateral side of the top surface. Each second spring 60 has a projection 70 for resting thereon. The second springs are similar to the first springs, but may be greater in size. The second springs 60 are typically positioned in cylindrical openings similar to those used for the first springs 50, although the cylindrical openings may not be necessary in some arrangements. With the arrangement shown in Figs. 1-10, a total of sixteen springs (twelve first springs and four second springs) are utilized on the outer periphery of the sample block 16. The number and specific arrangement of springs can be varied greatly depending on the specific application.

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20 It is desirable that the urging mechanism provide a substantially uniform force on the sample well tray in order to reduce undue bending of the sample well tray. As the force is more evenly distributed, more lightweight and thinner sample well trays may be used. Therefore, costs can be reduced for the sample well tray production and materials if the urging mechanism distributes the upward force in a substantially uniform manner. If few, large force points were used, the tray may become locally deformed in a way that could affect the handling of the tray later in the process. Lastly, the

application of a substantially uniform spring force around the periphery of the sample well tray may help reduce evaporation losses from locations adjacent the periphery of the sample well tray by ensuring that the sample well tray is firmly and evenly placed against the heated cover. Therefore, in one embodiment, it is preferable to provide a large number of substantially uniformly spaced springs for the urging mechanism.

Springs 50 and 60 of urging mechanism 18 provide an upward force on the sample well tray that is sufficient to overcome the sticking force caused by the cover and loosen the sample well tray from the sample block upon opening of the cover. The upward force applied by the springs should be less than the downward force applied by the cover or the cover will not remain closed. The downward force imparted by the cover is typically significantly greater than the upward force imparted by the springs in order to ensure good thermal contact between the sample wells of the sample well tray and the openings of the sample block.

An example of suitable type springs used in one embodiment of the urging mechanism is shown in Figs. 9A-9C and 10A-10C. The springs of this embodiment, by way of example only, are helical coil springs selected to impart sufficient force to urge the sample well tray away from and slightly out of the sample block after the cover is opened. In one example of the present invention shown in Figs. 9A-9C and 10A-10C, the first springs 50 have an outside diameter of 1.92mm, length of 6.3mm, and spring rate of 0.275kg/mm. During closing of the cover, these first springs 50 each compress 1.15mm thus imparting an ejecting force of 0.316kg each. In the same example, the second springs 60 have an outside diameter of 3.05mm, length of 9.53mm, and spring

rate of 0.987kg/mm. During closing of the cover, these second springs 60 each compress 1.55mm thus imparting an ejecting force of 1.53kg. In the present example, there are twelve first springs and four second springs, resulting in a total spring force applied to the sample well tray of 9.91kg. These numbers are by way of example only for one embodiment of the present invention. As is clear from the above description, a greater or lesser number of springs with different spring constants, shapes and sizes may be desirable in order to vary the upward force imparted by the urging mechanism upon opening of the cover, compared to the above example.

The particular springs used in the above example were made of stainless steel, however other suitable materials are also acceptable. The springs are preferably of a low thermal mass compared to the sample block and therefore do not materially affect the performance of the system. Therefore, the sample block and sample well tray maintain a substantially uniform temperature distribution that is not affected by the urging mechanism 18.

The operation of the heating apparatus for one typical embodiment of the present invention will now be more completely described below. First, the heated cover 12 of the thermal cycler is positioned in a first open position. A sample well tray with a predetermined amount of liquid sample in some or all of the sample wells is placed on top of the sample block. In the dual 384-well assembly shown in Figs. 1-10, two sample well trays are provided, one for each of the sample blocks. The sample well tray 16 typically includes either an adhesive film, a heat seal film, a gap pad, or individual caps for covering each of the sample wells 42 at the time of insertion into the thermal cycler.

The sample wells 42 are aligned with the sample block openings and inserted downward into the conical sample block openings 20. The heated cover is then slid so that it is placed over the sample well trays and sample block. The heated cover is then manually or automatically closed.

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As the heated cover closes, a heated platen (or the gap pad located below the platen) of the heated cover 12 presses down on the top of the sample wells to firmly press the sample wells 42 into the sample block openings 20, as best shown in Fig. 7. As the heated cover closes, the first and second springs 50 and 60 of the urging mechanism 18 are compressed by a bottom flat surface 58 of the sample well tray on the outside periphery of the sample wells 42. As the springs are compressed, the compression springs impart an upward force on the sample well tray 16 while the heated cover is in its closed position. While in the closed position, the thermal cycler then thermally cycles the liquid sample in the sample well tray to undergo a PCR or other type of chemical reaction.

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After the thermal cycling and/or other operations are completed, the heated cover 12 is opened (either manually or automatically). As the heated cover is opened, the platen (or gap pads) of the heated cover will no longer press against the top of the sample wells. Simultaneously, the springs of the urging mechanism 18 will impart an upward force on the bottom surface 58 of the sample well tray, thereby urging the sample wells 42 out of the sample block openings 20. The springs should impart sufficient force so that the sample well tray 16 will become loosened from the sample block 14 and be raised a slight distance in an upward direction. After the sample well

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tray is loosened from the sample block, the sample well tray may be robotically lifted out of and away from the sample block without any additional manual steps. As previously discussed, the provision of the urging mechanism allows the sample well tray to be more quickly and efficiently removed from the sample block.

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As is clear from the above description, the present invention includes a method of assisting in the removal of a sample well tray from a sample block. The method includes the steps of providing an initial downward force on a sample well tray by closing a cover. The initial downward force presses sample wells of the sample well tray into openings on a top surface of a sample block. The method further includes the step of providing an upward force on the sample well tray by a spring system positioned between the sample well tray and the sample block, the upward force being substantially smaller than the initial downward force. The cover is then opened to remove the initial downward force on the sample well tray, and the sample well tray is urged from the sample block by the upward force from the spring mechanism.

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The system and method according to the present invention reduces the amount of time that it takes to remove the sample well tray from the sample block. The urging mechanism arrangement allows the sample well tray to be automatically removed from the sample well block without unduly exposing an operator to the chemicals in the sample well tray which may occur during manual handling of sample well trays. The system and method according to the present invention are not limited by the examples shown above which are for purposes of illustration only.

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5 In another aspect, the present invention includes a heating apparatus of a second embodiment. In this embodiment, the apparatus includes a heated cover, a sample block having a plurality of openings, a sample well tray having a plurality of sample wells, a sample well tray holder for supporting the sample well tray, and an urging mechanism positioned between the sample block and the sample well tray holder to urge the sample well tray away from the sample block when the heated cover is moved from a closed position to an open position. As embodied herein and shown in Figs. 11-13, the heating apparatus 100 for biological samples includes a heated cover 110, a sample block 112, a sample well tray 114, a sample well tray holder 116, and an urging mechanism 118.

10 The heating apparatus of the embodiment shown in Figs. 11-13 is a 96-well PE Biosystems thermal cycler with optical detection capability, however, the heating apparatus is also suitable for other types of thermal cyclers with different numbers of wells, as well as those without optical detection capabilities. The present invention is suitable for a heating apparatus in which sample wells are pressed into a sample block by a cover. Similar to the first embodiment, the present invention is especially suitable for use in a heating apparatus with a heated cover.

15 In accordance with the present invention, the heating apparatus includes a heated cover. As embodied herein and shown in Figs. 11-13, the heated cover 110 is located above the sample block 112, sample well tray 114, and sample well tray holder 116. The heated cover is operable between an open position in which the heated cover

does not impart a downward force on the sample well tray, and a closed position where the heated cover imparts a downward force on the sample well tray.

In an exemplary embodiment shown in Figs. 11-13, the heated cover 110 includes a central cover portion 120 and an outside cover portion 122. In the embodiment shown in Fig. 12, the central cover portion 120 has a plurality of openings 124 for the optical detection of reactions that occur in the sample wells of the sample well tray. The present invention is also suitable for use in a thermal cycler without optical detection capabilities. In one preferred embodiment shown in Figs. 11-13, the outside cover portion 122 is movable in an upward and downward direction relative to the central cover portion 124. The movement of the outside cover portion 122 relative to the central cover portion 124 assists in isolating the spring force of an urging mechanism from the sample well tray during thermal cycling protocols.

The heated cover 110 of Figs. 11-13 also includes a plurality of distribution springs 126 for distributing the force of the central cover portion 120 onto the sample well tray 114. The distribution springs 126 also allow for the upward and downward motion of the outside cover portion 122 relative to the central cover portion 120. Each distribution spring 126 includes a pin (not shown) positioned inside of the helical spring. The pin passes through the central cover portion 120 and is connected to the outside cover portion 122 so that the central cover portion and outside cover portion are biased toward one another. A driving mechanism (not shown) drives the central cover portion 124 and outside cover portion 122 in a downward direction so that the heated cover

presses firmly on the sample well tray in a manner which will be described in greater detail below.

In accordance with the present invention, the heating apparatus includes a sample well tray and sample well tray holder for supporting the sample well tray. As embodied herein and shown in Figs. 11-13, the sample well tray 114 is a conventional sample well tray known in the art with a plurality of sample wells 115. In the embodiment shown in Figs. 11-13, the sample well tray is a 96-well tray, however the instant invention is applicable for use with sample well trays having any number of wells from one or two wells to several thousand. For example, the present invention is also particularly suitable for use with 384 and 60-well trays known in the art. The present invention is suitable for use with sample well trays having a variety of sizes and shapes. In the example shown in Figs. 11-13, the sample wells have a working volume of $200\mu\text{l}$, a diameter of 5.50mm and a depth of 20.0mm. The volume of the sample wells may vary anywhere from $0.1\mu\text{l}$ to thousands of microliters (μl), with a volume between 50 to $500\mu\text{l}$ being typical, with a volume of 100 to $200\mu\text{l}$ being most preferred. Similar to the embodiment of Figs. 1-10, the heating apparatus of Figs. 11-13 is also suitable for use with sample trays where the liquid sample is placed on a structure other than a sample well, such as a microscope slide or a frit.

In contrast to the embodiment of Figs. 1-10, the heating apparatus of Figs. 11-13 further includes a sample well tray holder 116 for supporting the sample well tray. The sample well tray holder 116 is in the shape of a flat plate with a main body portion 140

and an arm portion 142. In the example shown in the drawings, the main body portion 140 is in a rectangular shape. The main body portion 140 also defines a rectangular opening 146 for the sample well tray 114. The sample well tray holder is preferably made out of a material with poor heat conduction characteristics and a low thermal mass. In one embodiment, the material selected for the sample well tray holder is a polycarbonate. Other suitable materials are also acceptable.

In one embodiment, the arm portion 142 of the sample well tray holder 116 projects on the same plane as the main body portion 140, and is used for connection to a robotic manipulator (not shown). A robotic manipulator may grasp the arm portion 142 via the clamping mechanism 144 positioned on the end of the arm portion 142 and swing the main body portion into position to insert the sample well tray 114 into the heating apparatus. The robotic manipulator also allows for the sample well tray to be moved upward and downward over the sample block, and preferably initiates an additional downward movement on the sample tray holder to isolate the sample well tray from the urging mechanism when the cover is in its closed position, as will be described in greater detail.

The main body portion 140 of the sample well tray holder preferably includes a plurality of bosses 150 projecting upward from the top surface thereof. The bosses shown in the Figures are for purposes of illustration only, as the bosses can be of any variety of sizes, shapes, and designs. For example, the bosses could also be a ridge around the outside periphery of the opening for the sample well tray. The bosses could

also be significantly lengthened compared to those shown in Fig. 12. The function of the bosses will be described in greater detail below.

The rectangular opening 146 of the sample well tray holder is designed so that the sample well tray 114 may rest on the sample well tray holder 116. This is shown for example in the schematic of Figs. 13A-13C. The rectangular opening 146 is defined by a tapered wall 160 which tapers downward from the top surface 162 of the sample well tray holder 116. The opening defined by the tapered wall 160 is greater in length and width than the length and width of the sample well tray 114. The tapered wall 160 tapers until it meets a floor portion 164 which extends from the tapered wall 160. The floor portion 164 extends along the bottom surface 166 of the sample well tray holder. The floor portion 164 defines a rectangular opening that is smaller than the size of the sample well tray. When the sample well tray is placed in the rectangular opening 146, outer side walls 168 of the sample well tray rest on a top surface 170 of the floor portion. This is best shown in the schematic of Figs. 13A-13C. When the sample well tray 114 is placed in the rectangular opening 146 so that the sample well tray rests on the floor portion 164, the sample well tray 114 is free to move in an upward direction relative to the sample well tray holder 116. In the embodiment shown schematically in Figs. 13A-13C, the floor portion 164 is thinner than the remainder of the sample well tray holder 116. The sample well tray holder of Figs. 11-13 is shown for purposes of illustration only.

5 In accordance with the present invention, the heating apparatus includes a sample block including a plurality of openings for the sample wells of the sample well tray. As embodied herein and shown in Figs. 11-13, the sample block 112 includes a plurality of sample block openings 130 in a top surface 132 of the sample block. The openings are defined by conical side walls 134 similar to those described for Figs. 1-10 and a bottom surface 136. The sample block 112 is positioned in a base 200 for supporting the sample block. As best shown in Fig. 12, base 200 includes a raised surface 202, a first lower surface 204, a second lowered surface 206, and third lowered surface 208. The first lowered surface 204 is sized to accommodate the main body portion 140 of the sample well tray holder 116. Additionally, the first lowered surface 204 defines a recess for receiving the sample block 112 therein. The second and third lowered surfaces, 206 and 208, are sized to also accommodate the sample well tray holder. The first lowered surface 204 of the base is configured to engage the urging mechanism as will be described below.

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20 In accordance with the present invention, the heating apparatus includes an urging mechanism for urging the sample well tray out of the sample well block upon opening of the cover. As embodied herein and shown in Figs. 11-13, the urging mechanism 118 may include any suitable type of mechanism such as a spring device for pressing upward on the sample well tray holder and sample well tray when the heated cover is opened. In one embodiment, the urging mechanism 118 includes a plurality of springs. More particularly, the plurality of springs comprise leaf springs 180

5 attached to a bottom surface 166 of the sample well tray holder 116. The leaf springs, in one embodiment, are attached to the bottom surface 166 of the sample well tray holder. Alternately, the leaf springs could be attached to the sample well block. In the particular embodiment shown in Figs. 11-13, the leaf springs 180 were attached to the sample well tray holder, instead of the sample block, in order to make cleaning of the heating apparatus more easy. Additionally, the arrangement of the leaf springs on the sample well tray reduces the thermal effect of the leaf springs on the sample block, compared to if the leaf springs were attached to the sample block.

10 In the embodiment of Fig. 11, four leaf springs 180 are attached to the bottom surface 166 of the sample well tray holder 116. The four leaf springs are substantially symmetrically spaced around the sample well tray. Although, the Figures show four leaf springs, anywhere from one to several dozen leaf springs could be used with the present invention. It is desirable that the leaf spring be comprised of a non-corrosive material that will maintain reasonably constant spring characteristics. In one 15 embodiment, the material for the leaf spring is beryllium copper. Any other suitable material is also acceptable.

20 The urging mechanism of the present invention is not limited to the design shown in Figs. 11-13. The urging mechanism may also be made out of any variety of force imparting devices instead of the leaf springs shown in Figs. 11-13 such as coil springs, hydraulic dampeners, elastomeric springs, or other conventional spring devices. Leaf springs were selected in the particular embodiment because of the large distance

between the bottom surface 166 of the sample well tray 114 and the first lower surface 204 of the base 200. The use of a coil spring is possible with this configuration, however there may be a substantial amount of unsupported spring length if a coil spring is used. Therefore, types of springs besides coil springs may be desirable if the amount of unsupported spring length is substantial in the particular configuration.

The sample wells 115 of the embodiment of Figs. 11-13 may be covered by any of the conventional methods known in the art. For example, Fig. 12 shows a row of sample well caps 210 for covering the top of the sample wells 115. The caps may be individual, or grouped in rows of eight as shown in Fig. 12. Alternatively, instead of using caps, an adhesive film can be used to seal off the sample wells. Another typical type of seal known in the art is a heat seal film. Any of these known structures may be utilized for covering the sample wells.

In addition to the sample well covering or sealing method, a thin compliant cover may be placed between the heated cover and the top of the sample well tray. This compliant cover is similar to the gap pad that may be utilized in the Figs. 1-10 embodiment, but does not typically supply a seal to the top of the sample wells. In other embodiments, the compliant cover serves the function of the cover and gap pad. An example of a typical compliant cover is shown in Figs. 13A-13C, as reference number 212. The compliant cover 212 helps to evenly distribute the downward force imparted by the heated cover onto the sample well tray. The compliant cover may be made out of a polymeric, composite material or other material that can withstand the

high temperatures experienced during thermal cycling. The compliant cover of Figs. 11-13 is typically used in conjunction with the sealing methods (caps, adhesive tape, etc.) for the sample wells. The compliant cover typically includes detection holes 214 aligned with each of the sample wells 115 of the sample well tray 114. The detection holes 214 are also aligned with the openings 124 on the central cover portion 120 of the heated cover for allowing light emissions from the liquid sample to be detected by a detection apparatus (not shown).

The operation of the heating apparatus for one typical embodiment corresponding to Figs. 11-13 will now be more completely described below. First, the heated cover 12 of the thermal cycler is positioned in a first open position. The sample well tray 114 is then placed into the sample well tray holder 116 either manually or automatically. At this time the sample wells 115 of the sample well tray have already been filled with the appropriate biological liquid samples. The sample wells have also been sealed by the appropriate method, such as placement of caps 210 on the sample wells. The sample well tray holder 116 is then rotated by the robotic manipulator so that the sample well tray holder and sample well tray are positioned between the heated cover 110 and the sample block 112 as shown in Fig. 13A.

After the sample well tray holder and sample well tray are positioned as shown in Fig. 13A, the sample well tray holder 116 and sample well tray 114 are lowered so that the sample wells 115 are positioned inside the sample block openings 130. The sample well tray holder and sample well tray are lowered by either the robotic manipulator moving them downward or by pressing the heated cover 110 downward,

depending on the particular configuration. The heated cover 110 is moved downward by either manual or automatic operation, so that the sample wells 115 of the sample well tray 114 are pressed firmly into the openings 130 of the sample block as shown in Fig. 13B.

Fig. 13B illustrates the heated cover in a closed position, which will be referred to as the "seated" position. In the seated position, the leaf springs 180 are compressed between the sample well tray holder 116 and the first lowered surface 204 of the base. In this first lowered position or seated position shown in Fig. 13B, the bottom surface 166 of the sample well tray holder 116 is spaced by the distance of y_1 from the top surface 204 of the base. The top surface 170 of the floor portion 164 of the sample well tray holder is pressed against the bottom of the side wall 168 of the sample well tray by the spring force of leaf springs 180. The upward force imparted on the side wall of the sample well tray has a tendency to cause bending of the sample well tray.

The seated position shown in Fig. 13B is only obtained for a brief moment. In the preferred method of operation, a heated cover actuator (not shown) will press downward on the outside cover portion 122 of the heated cover 110 so that the sample well tray holder 116 will move slightly downward relative to the sample well tray 114 to the position shown in Fig. 13C. In this manner, the top surface 170 of the floor portion 164 will become spaced from the bottom of the side wall 168 in order to isolate the sample well tray 114 from the spring force generated by the leaf spring 180 while in the compressed position shown in Fig. 13C. The position shown in Fig. 13C will be referred to as the compressed position, because the leaf spring is compressed even farther so

that the spacing between the bottom surface 166 of the sample well tray holder 116 and the top surface 204 of the base is reduced to a measurement of y_2 . In the compressed position, the sample well tray holder 116 will not press upward on the side wall 168 thereby substantially preventing bending of the sample well tray 114. This reduces the amount of volume loss due to bending.

The heating apparatus is thermally cycled upon being positioned in the compressed position of Fig. 13C. After the apparatus has been thermally cycled, the mechanism for driving the heated cover downward is released in order to open the cover. The heated cover no longer contacts the top of the sample well tray. The leaf spring 180 simultaneously pushes the sample well tray holder 116 upward. The top surface 170 of the floor portion 164 then engages the bottom of the side wall 168 of the sample well tray 114, and pushes upward on the sample well tray. The force imparted on the sample well tray is sufficient to overcome the initial sticking force, and the sample well tray is loosened from the sample block. The sample well tray 114 is thus safely ejected from the sample block 112 so that the robotic manipulator may remove the sample well tray holder and sample well tray from the sample block.

It will be apparent to those skilled in the art that various modifications and variations can be made in the apparatus and method for ejecting a sample well tray from a sample tray, use of the apparatus of the present invention, and in construction of this apparatus, without departing from the scope or spirit of the invention. For instance, the system could be use in any variety of devices having a plurality of sample wells pressed into a sample block.

Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

WHAT IS CLAIMED IS:

1. A system for urging a sample well tray away from a sample block, comprising:

a sample block having a plurality of openings for receiving sample wells of a sample well tray therein; and

at least one urging mechanism interposed between the sample block and the sample well tray to urge the sample wells away from the openings in the sample block.
2. The system of claim 1, wherein said urging mechanism is engageable with the sample well tray.
3. The system of claim 1, wherein said urging mechanism comprises a plurality of spring devices.
4. The system of claim 3, wherein at least one of said spring devices is positioned about an outer periphery of the sample block in a region outside of the openings in the sample block.
5. The system of claim 4, the sample block further comprising at least one receiving portion for receiving a portion of said at least one spring device.

6. The system of claim 5, wherein said at least one spring device comprises a coil spring.

7. The system of claim 6, wherein the receiving portion comprises a cylindrical opening for accommodating a portion of the coil spring.

8. The system of claim 3, wherein said plurality of spring devices are positioned substantially symmetric around the periphery of the sample block.

9. The system of claim 1, wherein the urging mechanism is positioned between the sample block and the sample well tray.

10. The system of claim 1, wherein the urging mechanism comprises a plurality of spring devices spaced around an outer periphery of a top surface of the sample block, said spring devices being accommodated in cylindrical openings in the sample block, said spring devices engaging a bottom surface of the sample well tray in order to disengage the sample well tray from the sample block upon opening of a cover for the system.

11. The system of claim 1, further comprising a sample well tray holder for holding the sample well tray, said sample well tray being movable relative to the sample well tray holder.

12. The system of claim 11, wherein said urging mechanism biases the sample well tray holder away from the sample block to thereby urge the sample wells out of the openings in the sample block upon the opening of a cover for the sample well tray.

13. The system of claim 12, wherein said urging mechanism comprises a plurality of spring devices.

14. The system of claim 13, wherein a portion of the spring devices are attached to the sample well tray holder.

15. The system of claim 14, wherein the spring devices are positioned substantially uniformly around an opening for the sample well tray on the bottom of the sample well tray holder.

16. The system of claim 15, comprising four of said spring devices.

17. The system of claim 15, wherein said spring devices comprise leaf springs.

18. The system of claim 1, wherein the sample wells received by the sample block are sized to have a fluid volume in the range of 10 to 500 μ L.

19. A heating apparatus for biological samples, comprising:

a cover;

a sample block having a plurality of openings in a top portion thereof for receiving a sample well tray having a plurality of sample wells; and

an urging mechanism positionable between the sample block and the sample well tray to urge the sample well tray away from the sample block when the cover is moved from a closed position toward an open position,

wherein said cover imparts a downward force on the top of the sample well tray to press the sample wells into the openings of the sample block when the cover is moved toward a closed position, said urging mechanism imparting an upward force on the sample well tray, and wherein said downward force imparted by the cover is sufficient to retain the sample well tray against the sample block when the cover is in said closed position.

20. The heating apparatus of claim 19, wherein a sample well tray is positionable between the cover and the sample block when the cover is in a closed position.

21. The heating apparatus of claim 20, wherein the urging mechanism comprises at least one spring device engageable with the sample well tray and the sample block.

22. The heating apparatus of claim 21, wherein the at least one spring device engages the sample block, the at least one spring device being positioned on a surface of the sample block radially outside of the openings in the sample block.

23. The heating apparatus of claim 22, wherein the sample block further comprises a plurality of cylindrical spring openings for receiving a plurality of the spring devices of the urging mechanism.

24. The heating apparatus of claim 21, further comprising a sample well tray holder, the sample well tray holder supporting the sample well tray, the sample well tray being movable relative to the sample well tray holder.

25. The heating apparatus of claim 24, wherein the urging mechanism is positioned on a bottom surface of the sample well tray holder.

26. The heating apparatus of claim 25, wherein the urging mechanism includes a plurality of springs.

27. The heating apparatus of claim 26, wherein the sample well tray holder may be pressed downward by an outside portion of the heated cover so that the sample well tray becomes disengaged from the sample well tray holder, the urging mechanism no longer imparting an upward force on the sample well tray in this position.

28. The heating apparatus of claim 27, wherein the sample well tray receives said upward force from the sample well tray holder when the outside portion of the heated cover is no longer pressed downward so that the sample well tray holder engages the sample well tray.

29. A system for urging a sample tray for biological material away from a base of the system, comprising:

a base configured to be engageable with a sample tray; and

at least one urging mechanism interposed between the base and the sample tray to urge the sample tray away from the base.

30. The system of claim 29, wherein the base includes a plurality of openings for receiving sample wells of the sample tray, said sample wells being urged away from the base during operation of the urging mechanism.

31. The system of claim 29, wherein the urging mechanism engages a sample tray with a flat upper surface for receiving samples of a biological material.

32. A method of manipulating a sample well tray with respect to a sample block, comprising the steps of:

providing an initial downward force on a sample well tray, said initial downward force pressing sample wells of the sample well tray into openings on a top surface of a sample block; and

providing an upward force on the sample well tray, the upward force being provided by an urging mechanism interposed between the sample block and sample well tray.

33. The method of manipulation of claim 32, further comprising the steps of reducing the initial downward force on the sample well tray, and urging said sample well tray from the sample block by an upward force between the sample well tray and the sample block.

34. The method of manipulating of claim 33, further comprising the step of removing the sample well tray from the sample block by a robotic mechanism.

35. The method of manipulating of claim 32, wherein the step of providing an upward force on the sample well tray is performed by a spring system of the urging mechanism including at least one spring device in communication with the sample block.

36. The method of manipulating of claim 35, wherein during the step of providing an upward force on the sample well tray, a plurality of spring devices engage with the sample well tray.

37. The method of manipulating of claim 35, wherein during the step of providing an upward force on the sample well tray, a sample well tray holder is provided for pressing the sample well tray in an upward direction.

38. The method of manipulating of claim 37, wherein prior to the step of providing an upward force on the sample well tray, the upward force imparted on the sample well tray holder by the spring system is substantially isolated from the sample well tray, so that substantially no upward force is imparted on the sample well tray holder by the sample well tray during a heating procedure performed by the apparatus.

ABSTRACT

The invention includes a heating apparatus for biological samples. The heating apparatus of the present invention includes a cover, a sample block having a plurality of openings in a top portion thereof for receiving a sample well tray having a plurality of sample wells, and an urging mechanism. The urging mechanism is positionable between the sample block and the sample well tray to urge the sample well tray away from the sample block when the cover is moved from a closed position toward an open position. The cover imparts a downward force on the top of the sample well tray to press the sample wells into the openings of the sample block when the heated cover is moved toward a closed position. The urging mechanism imparts an upward force on the sample well tray. The downward force imparted by the heated cover is sufficient to retain the sample well tray against the sample block when the cover is in the closed position.



FIG. 1

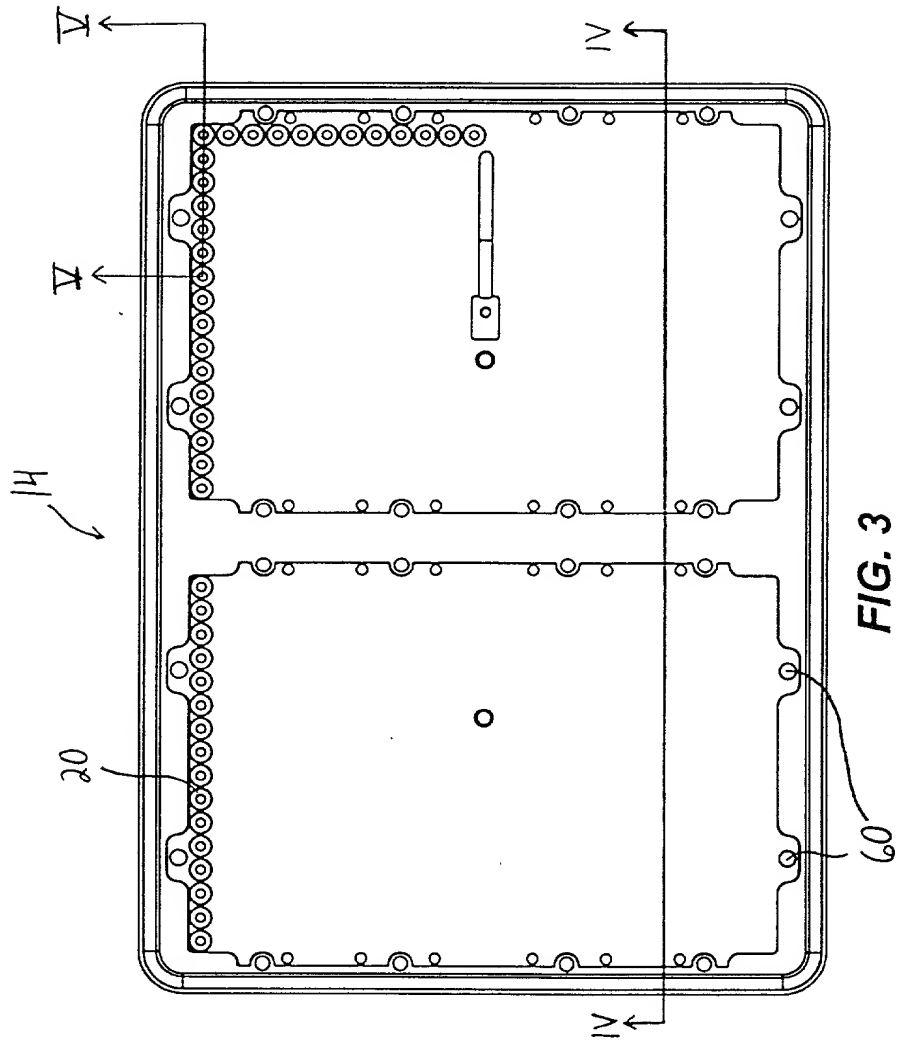


FIG. 3

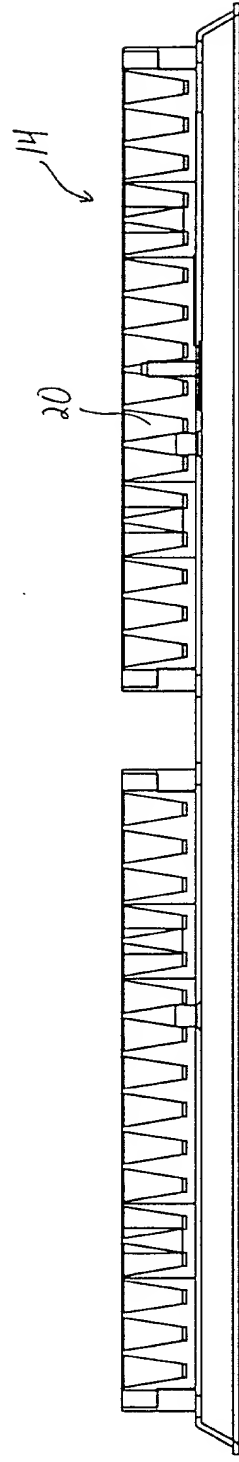


FIG. 4

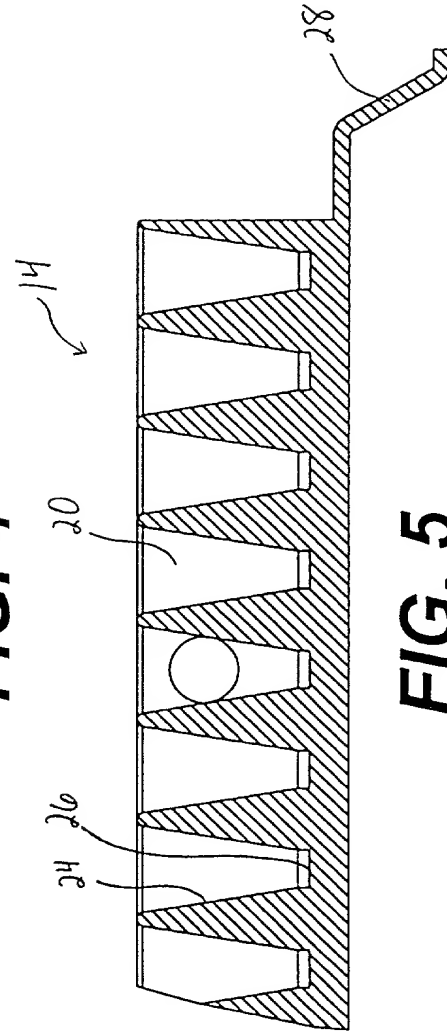


FIG. 5

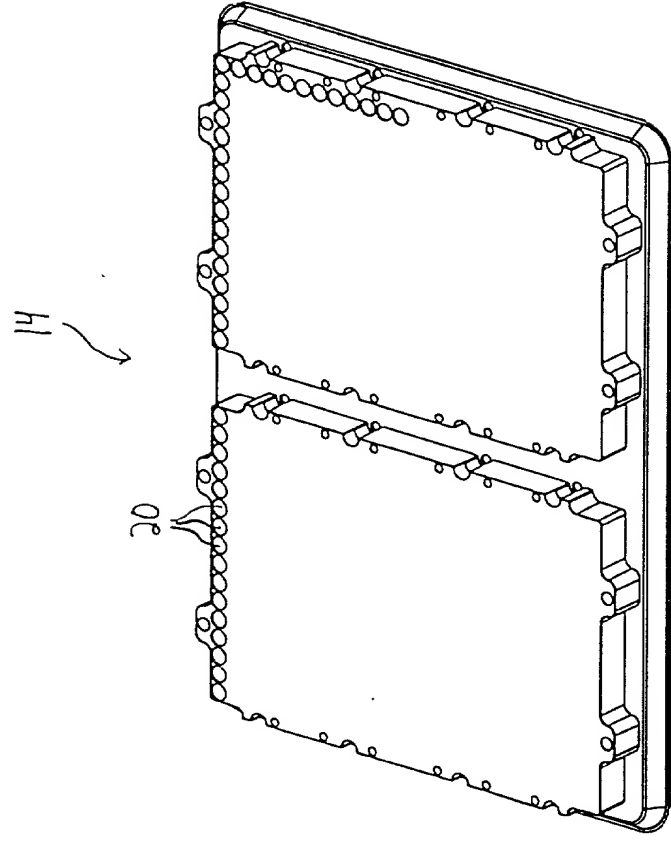


FIG. 6

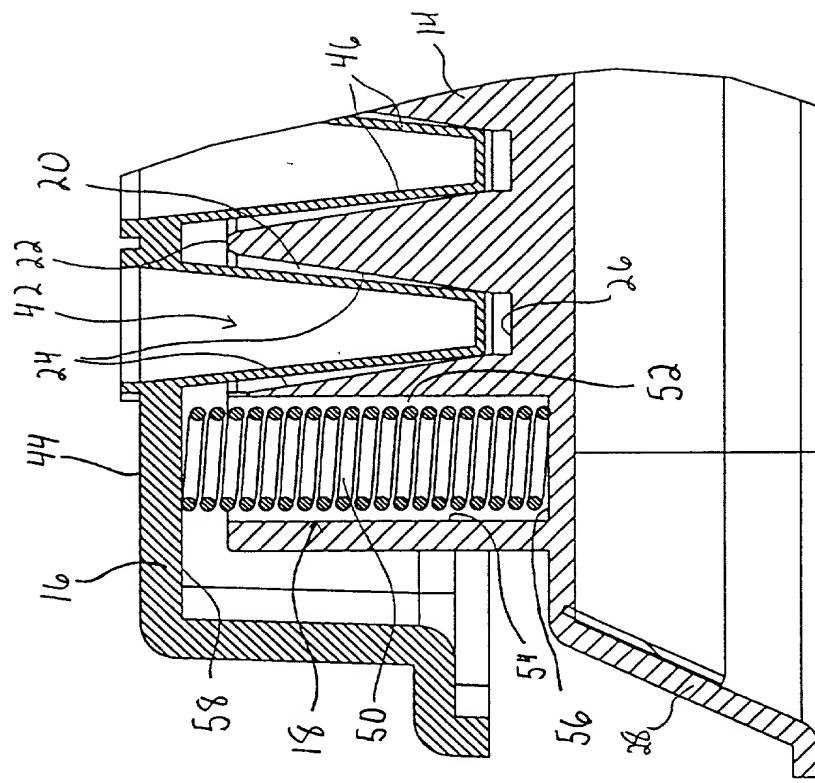


FIG. 7

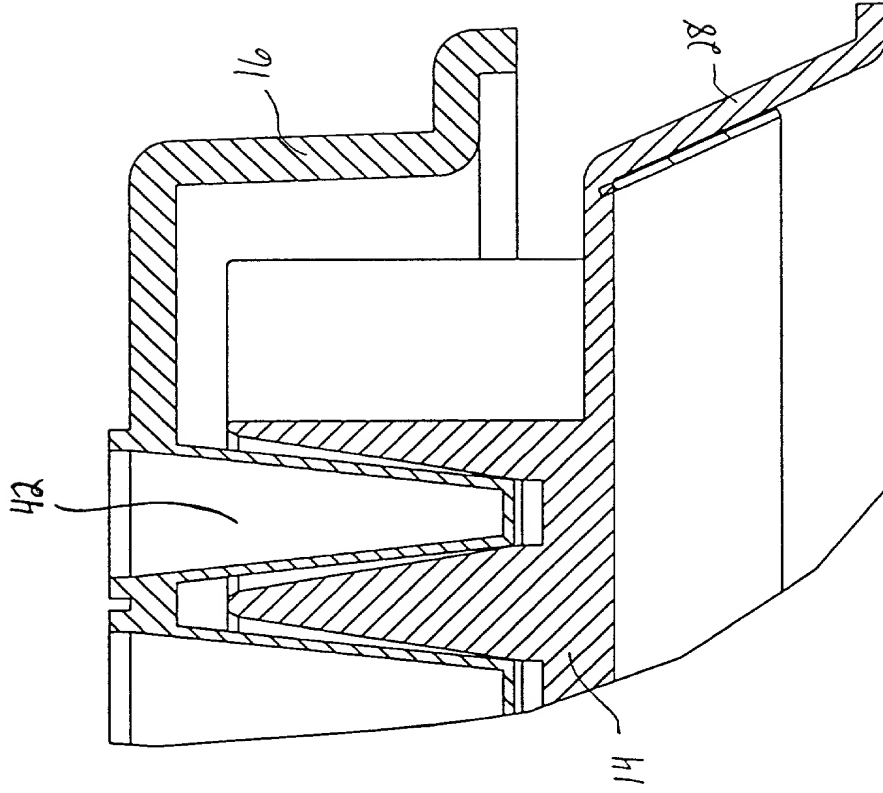


FIG. 8

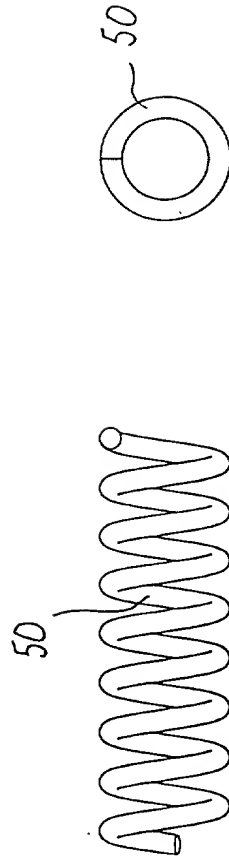


FIG. 9A

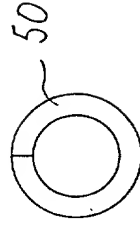


FIG. 9B

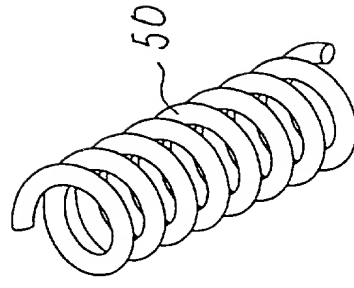


FIG. 9C

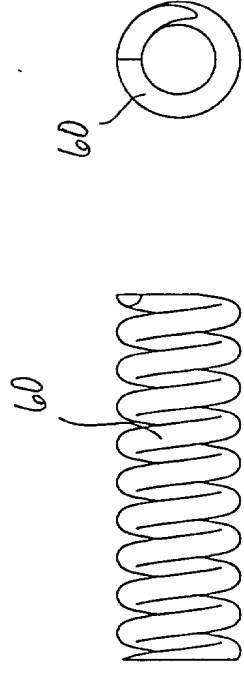


FIG. 10A

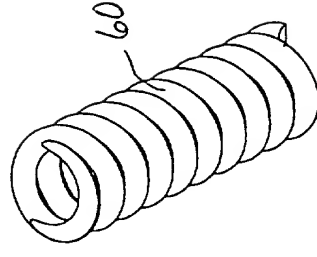


FIG. 10C

FIG. 11

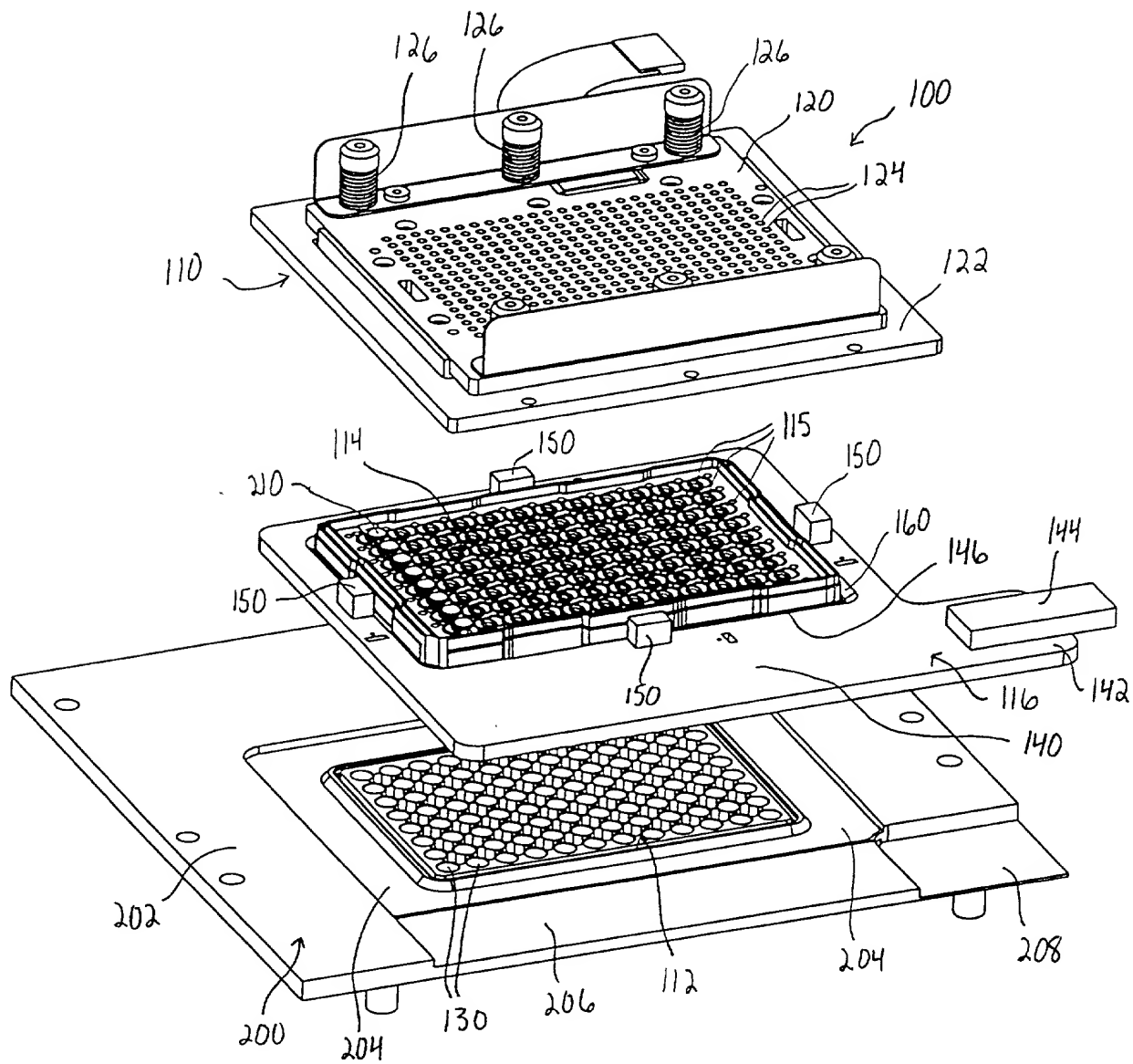


FIG. 12

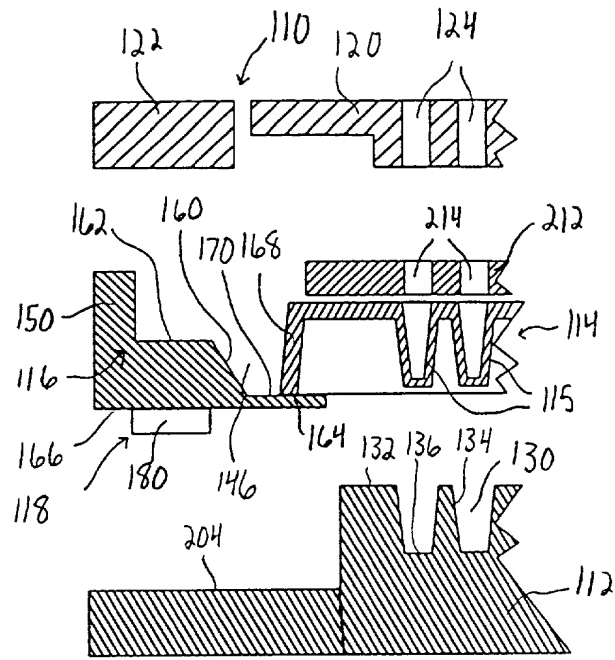


FIG. 13A

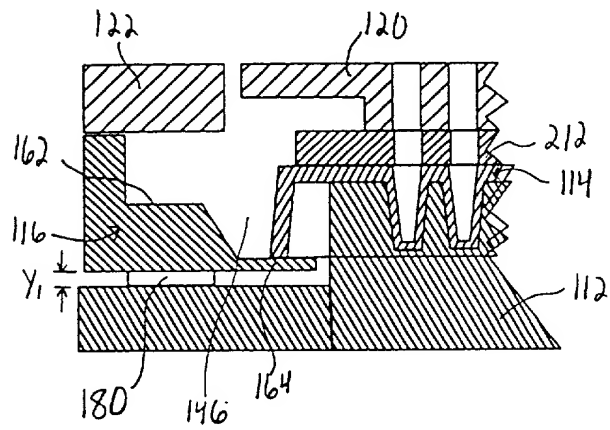


FIG. 13B

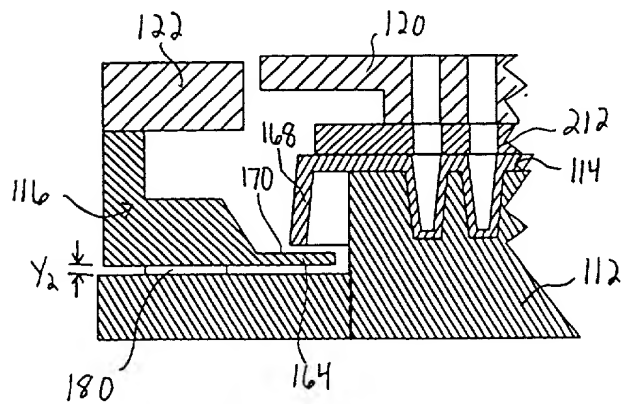


FIG. 13C